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Interstitial Mycosis Fungoides With Lichen Sclerosus–Like Clinical and Histopathological Features

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Abstract: Mycosis fungoides (MF) simulates a variety of dermatologic disorders histopathologically and clinically, well deserving the designation of a great mimicker. Interstitial MF is a rare, but well-recognized histopathological variant resembling the interstitial form of granuloma annulare or the inflammatory phase of morphea. From a clinical standpoint, MF can have a wide array of manifestations, including an anecdotal presentation with lesions clinically suggestive of lichen sclerosus (LS). We herein report a 25-year-old man with a history of patch-stage MF who later developed widespread LS-like lesions histopathologically consistent with interstitial MF. In some biopsies, additional features resembling LS were discerned. We think that our case might represent a unique variant of interstitial MF presenting with LS-like lesions. The diagnostic challenge arising from this uncommon presentation is discussed together with review of the literature.

Key Words: interstitial mycosis fungoides, lichen sclerosus

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INTRODUCTION

Mycosis fungoides (MF), the most common form of primary cutaneous lymphoma, remains a great diagnostic challenge because it exhibits a broad spectrum of clinical, histological, and immunophenotypic variants.[1–3] It can manifest as an interstitial lymphocytic infiltrate simulating the interstitial form of granuloma annulare or the inflammatory phase of morphea; this rare histological pattern has been termed interstitial MF. Although the histopathological and immunophenotypical features of this variant have been studied to some extent,[4–7] its clinical implications remain to be established.

Lichen sclerosus (LS) is among the many diseases that should be considered within the clinical and histopathological differential diagnosis of MF. LS, both in its genital and extragenital forms, can histopathologically mimic MF, creating a potential diagnostic pitfall.[3,8–12] However, isolated cases of overlap between MF and LS,[13] and MF clinically presenting with lesions resembling LS,[14] have also been described (Table 1), further complicating the interplay between these 2 entities.

Here, we report on a 25-year-old man with a history of patch-stage MF who returned to clinic after 15 months, presenting with widespread LS-like lesions histopathologically consistent with interstitial MF. In addition, some of the biopsies revealed features resembling those of LS. We discuss the diagnostic problem in our case and review the literature.

CASE REPORT

A 25-year-old man initially presented with widespread, slightly erythematous, finely scaling patches involving his trunk and arms (Fig. 1A). He reported a 5-year history of mild pruritus and dry skin, gaining minimal symptomatic relief from topical corticosteroids. Clinical appearance was that of an acquired ichthyosis, and MF had to be excluded. After the histological diagnosis of MF (patch-stage) (Fig. 1B), narrowband ultraviolet B (UVB) therapy was commenced. After a short course of phototherapy, new patch lesions developed that were histopathologically compatible with MF, as well. Narrowband UVB was switched to psoralen and UVA (PUVA); however, the patient did not tolerate the latter treatment because of gastrointestinal disturbance and was lost to follow-up. He returned 15 months later with ivory-colored sclerotic lesions on a slightly erythematous background covering over 80% of body surface area, clinically suggestive of generalized LS. At this second presentation, the clinical picture was mainly of a widespread LS (Figs. 2A–C). The results of the histopathological, immunohistochemical, and molecular studies revealed findings compatible with interstitial MF; therefore, clinical staging investigations were performed that revealed axillary and inguinal lymphadenopathies with a high uptake on positron emission tomography/computed tomography. However, excisional biopsy of the left inguinal lymph node was consistent with dermatopathic lymphadenopathy (N1). A combination therapy with oral acitretin, PUVA, and subcutaneous interferon α-2a was started, but, 2 months later, dermatologic treatments had to be stopped because the patient presented to the emergency department with cardiac arrest that was attributed to arrhythmogenic right ventricular dysplasia, necessitating implantation of a cardiac defibrillator. The initial concern about the possibility that interferon α-2a could have been a contributing factor for this cardiac event was disputed after consultation with the department of cardiology. Because there was no contraindication for any type of treatment from a cardiological point of view, combination therapy with acitretin, PUVA, and interferon α-2a was reinitiated, but the patient could not tolerate these treatments and abandoned all of them successively.

At present, 3 years after initial presentation, the widespread LS-like lesions persist. The patient is off treatment for his skin disease because of his dissatisfaction with the previous treatments.

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The authors declare no conflicts of interest.

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TABLE 1. Literature Review of the Cases Demonstrating Overlapping Clinicopathologic Features Between LS and MF

Reference	No. Cases	Age (yrs), Sex	Localization of Lesion(s)	Clinical Impression	Histopathology	T-Cell Clonality	Final Diagnosis After Clinicopathologic Correlation
Reddy and Bhawan[3]	1	NM	NM	LS	LS/MF overlap	Polyclonal	LS
Citarella et al[9]	9	7–75, M:8 and F:1	Genital	LS	MF (with signs of LS present only focally, if ever)	Eight cases polyclonal, 1 case monoclonal	LS
Suchak et al[10]	1	27, M	Extragenital	LS	Initial biopsy: MF; repeat biopsy from the same lesion 3 mo later: LS	Polyclonal	LS
Arps et al[11]	1	38, M	Genital	LS (phimosis)	MF	Monoclonal	LS
Magro et al[13]	1	60, F	Extragenital	Some lesions: LS/morphea; some others: MF	LS/MF overlap	NM	LS/MF overlap
Parera et al[14]	1	44, F	Extragenital	Initially MF, later additional lymphomatoid papulosis followed by new-onset LS	Histopathological features suspicious for both MF and LS	Biopsies from MF, lymphomatoid papulosis, and LS-like lesions monoclonal showing the same T-cell clone	MF (LS-like clinical variant)
This case	1	25, M	Widespread	Initial presentation acquired ichthyosis or MF; second presentation acquired LS	Initial presentation: patch-stage MF; second presentation: interstitial MF accompanied by LS-like features	Biopsy at initial presentation polyclonal; 2 biopsies from different lesions at second presentation monoclonal showing the same T-cell clone	MF (with LS-like clinical and histopathological features)

F, female; M, male; NM, not mentioned.

He is in regular follow-up by the departments of dermatology, hematology, and cardiology. Extracorporeal photopheresis has been planned.

MATERIALS AND METHODS

A total of 7 punch biopsies (2 at initial presentation, 2 at the time of exacerbation during narrowband UVB therapy, and another 3 at the second presentation of the patient when he returned to clinic after 15 months) were performed. Tissues were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and eosin–stained sections with a thickness of 4 μm were prepared. Immunohistochemical studies were performed on formalin-fixed paraffin-embedded tissue using a panel of monoclonal antibodies for CD3 (1:75, clone E272; Biocare Medical, Concord, CA), CD4 (1:20, clone 1F6; Novocastro, Buffalo Grove, IL), CD2 (1:100, clone AB75; Novocastro), CD5 (1:100, clone SP19; Thermo Scientific, Fremont, CA), CD7 (1:40, clone 7C03; Thermo Scientific), CD8 (1:40, clone 1A5; Novocastro), CD20 (1:250, clone L26; Thermo Scientific), and CD68 (1:1600, clone KP1; Dako, Carpinteria, CA) with Ventana Benchmark XT Immunostainer. Appropriate positive controls were included. Colloidal iron and Alcian blue stains were used to demonstrate the mucin accumulation. T-cell receptor (TCR)-γ genes clonality study was performed on 3 biopsy specimens using BIOMED-2 primers as described elsewhere.[15]

RESULTS

Histopathological Features

The first 2 biopsies were taken from erythematous patch lesions located on the right arm and on the lateral trunk (Fig. 1A) at the initial presentation of the patient. These 2 skin biopsies showed mainly superficial, partially band-like infiltrate, with focal areas of epidermotropism (Fig. 1B). The lymphocytes had hyperchromatic nuclei with slightly convoluted outlines. In the reticular dermis between a few collagen bundles, sparse lymphocytes were also detected. According to these histopathological findings, a diagnosis of patch-stage MF was made. After a short period of phototherapy, 2 more biopsies were taken, demonstrating similar features with the first 2 biopsies. At the second presentation of the patient with widespread LS-like lesions, 3 biopsies were performed from the sclerotic lesions on the subscapular region (Fig. 2B), on the abdomen (Fig. 2C), and the right thigh. The ones taken from the subscapular region and the right thigh were similar. Underneath the atrophic epidermis, there was a band-like infiltration, composed of small- to medium-sized

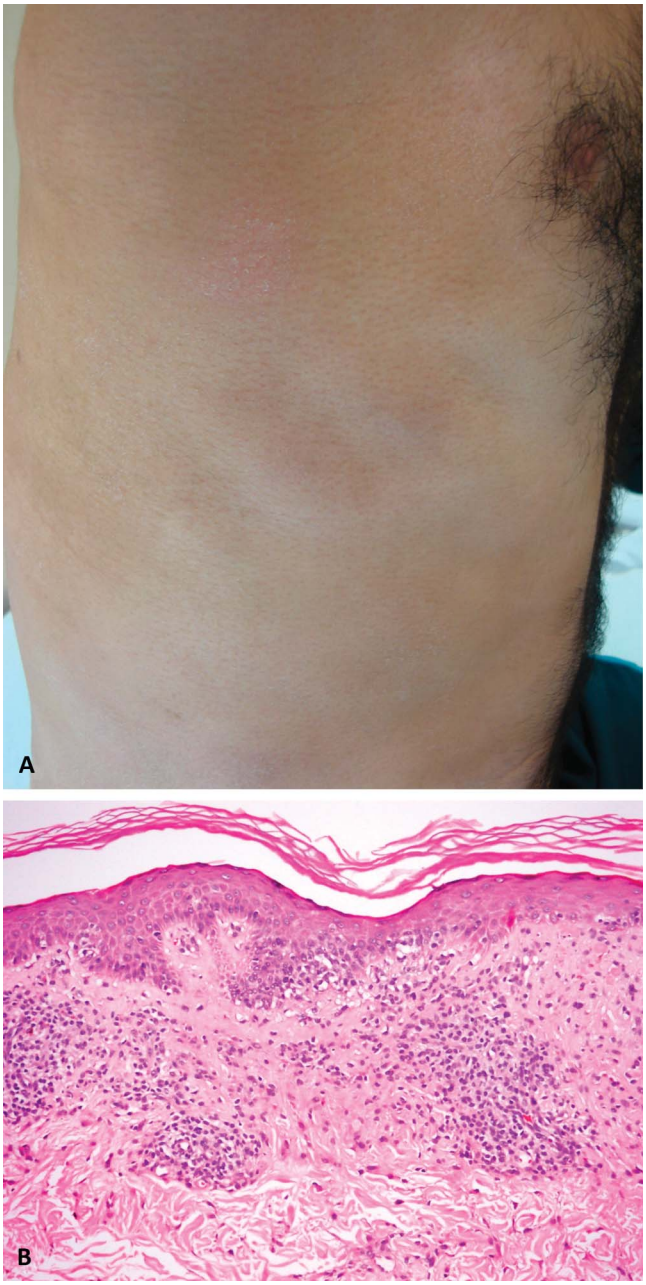

FIGURE 1. Erythematous, finely scaling patches with xerosis on the lateral trunk at initial presentation (A). Within the acanthotic epidermis, there are some atypical lymphocytes. Note the partially band-like lymphoid infiltration in the upper dermis (hematoxylin and eosin, ×100) (B).

lymphocytes, with hyperchromatic and slightly convoluted nuclei (Fig. 3A). At the lower parts of the epidermis, there were atypical lymphocytes, arranged in either solitary units with perinuclear haloes or in small collections. Wiry collagen was detected in the papillary dermis entrapped within the infiltration. In the reticular dermis, there was an interstitial infiltration of atypical lymphocytes between the collagen bundles, reminiscent of interstitial granuloma annulare or inflammatory stage of morphea (Fig. 3B). However, no mucin accumulation was seen and there were no accompanying plasma cells, epithelioid histiocytes, or multinucleated giant cells. The remaining biopsy taken from the abdomen revealed a hyperkeratotic epidermis with some areas of hydropic degeneration at the basal cell layer. In a small area, there was even a subepidermal detachment. Underneath the epidermis, homogenization and edema of the papillary collagen bundles was seen (Fig. 4A). In the reticular dermis, as in the other biopsy specimens, an interstitial infiltrate composed of small- to medium-sized atypical lymphocytes between the collagen bundles was detected (Fig. 4B). The histopathological features in these last 3 biopsies taken at the second presentation of the patient were consistent with interstitial MF, with the last one taken from the abdomen showing features of LS.

Immunohistochemical Findings

Immunohistochemistry performed on the biopsy specimens taken from the sclerotic lesions at the second presentation of the patient confirmed that the interstitial cells were lymphocytes, showing a T-cell phenotype ($CD3^+$, $CD5^+$, $CD2^+$) with loss of CD7. Those lymphocytes in the epidermis and papillary dermis demonstrated the same phenotype with a CD4/CD8 ratio close to each other. There were only a few $CD68^+$ histiocytes and rare $CD20^+$ B cells in the dermal infiltrate.

Molecular Biological Findings

Monoclonal rearrangement of TCR-γ genes could be detected in the biopsies taken from the subscapular region and the abdomen when the patient returned with widespread LS-like lesions at the second presentation. The sequencing of the amplified products demonstrated that the same T-cell clone was present in both biopsies. In the biopsy taken from the lateral trunk at the initial presentation, no monoclonal rearrangement of TCR-γ genes could be detected.

DISCUSSION

Interstitial MF is a rare histopathological variant of MF that presents as an interstitial dermal infiltrate consisting of a predominant population of T cells admixed with few histiocytes.[4] Several histopathological and immunohistochemical clues help to distinguish interstitial MF from its major histopathological simulants, interstitial granuloma annulare, and inflammatory morphea. Interstitial MF is characterized by a preponderance of T cells, whereas in interstitial granuloma annulare a more prominent histiocytic infiltrate has been described, highlighting the importance of immunohistochemistry for CD3 and CD68 in differential diagnosis. Mucin deposition in the interstitial dermis, a feature suggestive of interstitial granuloma annulare, may be potentially misleading because it has also been observed in some cases of interstitial MF.[4] On the other hand, inflammatory morphea is differentiated by the relative predominance of B cells and plasma cells in the interstitium.[4–6] In our case, T cells predominated over histiocytes and B cells. Plasma cells were mostly absent in the interstitium and no dermal mucin was

FIGURE 2. A–C, Generalized, white sclerotic lesions on a slightly erythematous background, clinically suggestive of LS, noted approximately 1.5 years after initial presentation.

detected, favoring a diagnosis of interstitial MF. The diagnosis of MF was further supported by the history of MF at the initial presentation, slight nuclear atypia of the lymphocytes, and demonstration of the same T-cell clone in 2 different biopsies. However, it should be kept in mind that monoclonality is not diagnostic of a neoplastic process per se, but only supportive in the appropriate clinicopathological context. Besides, a monoclonal population of T cells was also described in other diseases such as LS[8,9] and granuloma annulare[16]; thus, results of molecular studies should always be interpreted with caution. Similarly, absence of clonality in the initial biopsy does not necessarily rule out MF in our case because a clonal T-cell population is only found in half of the biopsies in early-stage MF lesions.[2]

In addition to the aforementioned histopathological findings compatible with interstitial MF, our case had unusual LS-like clinical and histopathological features deserving further discussion. LS and MF can be related in 2 ways (Table 1). Firstly, LS is a histologic mimicker of MF.[3,8–12] In a subgroup of LS histologically devoid of sclerosis, differential diagnosis may be even more difficult and based on subtle diagnostic clues, as demonstrated by Weyers.[12] Citarella et al described 9 cases of genital LS with histopathological features simulating early MF. Moreover, a monoclonal TCR-γ rearrangement was demonstrated by polymerase chain reaction in one of the 9 patients. However, all lesions were located in the genital area, such as the foreskin, glans, or labia, and no additional extragenital lesions were present. The importance of clinicopathological correlation in patients presenting with lesions consistent with LS clinically, but suggesting MF histologically was emphasized.[9] Apart from genital LS, extragenital LS mimicking MF histologically had also been described by Suchak et al.[10] Despite the well-described histologic findings suggestive of MF in these articles by Citarella et al[9] and Suchak et al,[10] there was no doubt about the diagnosis of LS in either of them because there were no other lesions clinically typical of MF. Our case, however, presented initially with xerotic, slightly erythematous patches on the trunk and arms without any genital involvement and presumptive clinical diagnosis of MF was confirmed histologically. His second presentation 15 months later was different, and LS would have been the most likely clinical diagnosis unless the patient had a previous diagnosis of MF and in addition features of interstitial MF were present in other biopsies.

Secondly, MF can present clinically with LS-like lesions as has been reported by Parera et al[14] who described a 44-year-old woman with a history of typical MF lesions and lymphomatoid papulosis who later developed lesions highly suggestive of LS in previously uninvolved areas. The biopsies taken from the typical lesions of MF and LS-like lesions were all consistent with MF; moreover, TCR-γ amplification study disclosed the same T-cell clone. Our patient, similarly, had a previous diagnosis of MF and

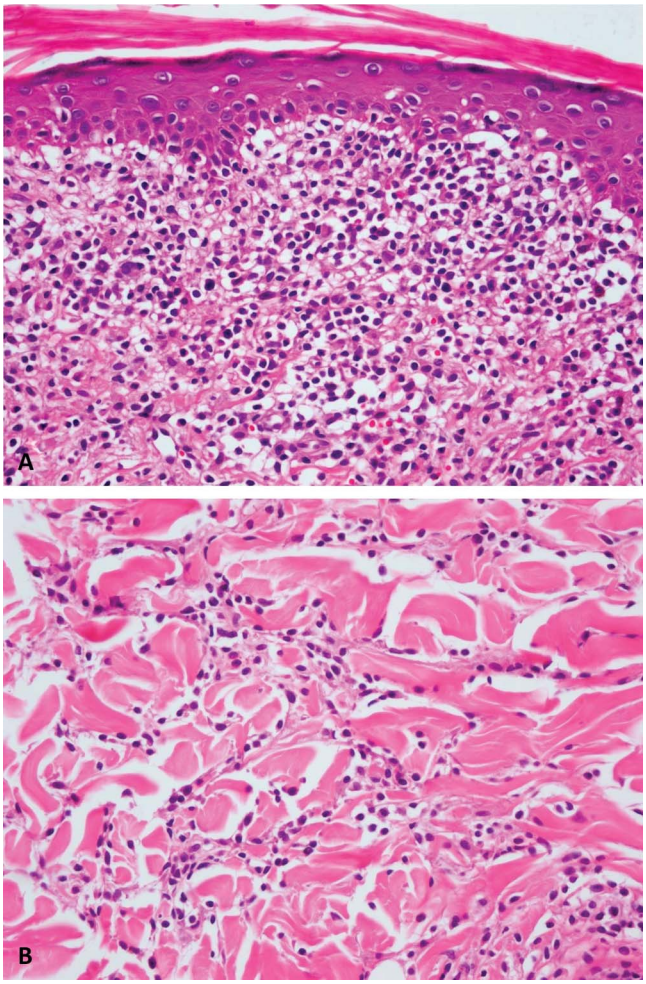

FIGURE 3. Histopathological examination of the biopsy taken from the subscapular region at the second presentation of the patient reveals small- and medium-sized, convoluted atypical lymphocytes, displaying epidermotropism (H&E, ×200) (A). Interstitial infiltrate among the collagen bundles, composed of small- and medium-sized atypical lymphocytes (H&E, ×200) (B). H&E, hematoxylin and eosin.

developed LS-like lesions in time, which were also consistent with MF. Supporting this diagnosis, monoclonality was demonstrated in these lesions. However, unlike the case of Parera et al,[14] LS-like clinical presentation of MF was associated with an interstitial pattern of MF in our case. Moreover, an overlap between MF and LS has also been reported in a patient who had initial lesions consistent with LS but later developed MF-like histologic features. This case was considered to represent an example of cutaneous T-cell lymphoma arising on a background of connective tissue disease.[13]

This case has several unusual features. One is the histological presentation as interstitial MF, a rarely described histologic pattern of MF, accompanied by LS-like features. Second is the striking clinical appearance. We are unaware of any similar case of MF in literature presenting with such a widespread distribution of LS-like lesions. None of the

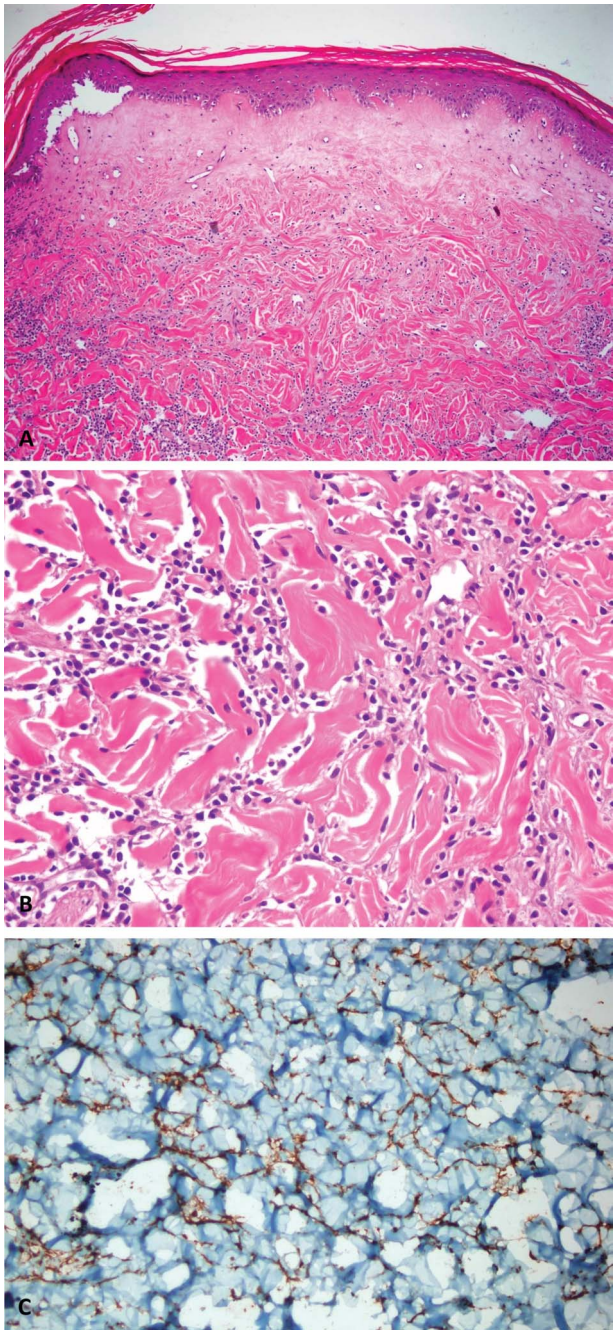

FIGURE 4. Histopathological and immunohistochemical features of the biopsy taken from a clinically LS-like lesion in the abdomen at the second presentation of the patient. Underneath the epidermis with some hydropic degeneration at the basal cell layer, there are edematous homogenized collagen bundles in the upper dermis, histopathologically suggestive of LS. These findings are accompanied by features of interstitial MF in the dermis as seen in the other biopsies (H&E, ×100) (A). Interstitial infiltrate composed of sparse histiocytes and small- to medium-sized lymphocytes with dark chromatin. These findings are consistent with interstitial MF, similar to the other biopsies (H&E, ×200) (B). Phenotypically, half of the lymphocytes express CD4 (C). H&E, hematoxylin and eosin.

biopsies revealed a histological picture of *genuine* LS per se; in other words, LS-like changes, when present, were always accompanied by a predominant background of interstitial MF. This finding, together with the demonstration of an identical T-cell clone in 2 different biopsies, indicates that the findings in our patient represent an example of interstitial MF manifesting in part with clinical and histological features of LS.

In conclusion, the protean manifestations of MF continue to pose a great diagnostic challenge to dermatologists and dermatopathologists alike. MF can present with clinical and histologic LS-like features in combination with interstitial MF, and clinicopathological correlation is of paramount importance for correct diagnosis.

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